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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/235,875	01/22/1999	LARA MADISON	MBX020	2296

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EXAMINER	
KALLIS, RUSSELL	
ART UNIT	PAPER NUMBER
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/235,875	Applicant(s) MADISON ET AL.	
	Examiner Russell Kallis	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27 and 31-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 31-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. Claims 1-27, 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

2. Claims are drawn to a method for the biological production of polyhydroxyalkanoate containing 3-hydroxyhexanoate, comprising growing a transgenic bacterium or transgenic plant transformed with at least one bacterial gene encoding an enzyme useful in the production of PHAs and transgenic bacteria and plants comprising said DNA. The enzymes set forth in the claims are; a PHA polymerase incorporating C6 substrates, a D-specific enoyl-CoA hydratase, the enzymes in a butyrate fermentation pathway, a broad range reductase, a polymerase that accepts 3-hydroxyhexanoyl CoA, a thiolase accepting acetoacetyl CoA, thiolases specific for 3-ketohexanoyl CoA, a reductase active on 3-ketohexanoyl CoA and 3-hydroxyhexanoyl CoA, one or more fatty biosynthethic enzymes, and enzymes that epimerize S-3 hydroxyhexanoyl CoA from the *Pseudomonas putida* FaoAB complex.

Applicant does not describe the composition or structure for any of the genes of the generic functional categories of bacterial enzymes set forth in the claims. Since the specification only provides a characterization of what the genes do, rather than their structural features it is unclear whether the inventor had possession of the claimed invention at the time of filing of the application.

The disclosure of a gene name describing a genetic locus or an abbreviated assessment of a phenotypic effect associated with a mutation or a functional name used to describe the specific activity of an enzyme was discussed with respect to its satisfying the written description requirement of 35 U.S.C. 112 1st paragraph.

The Federal Circuit has recently clarified the application of the written description requirement to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405.

The court also stated that a generic statement such as "Vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from the others, except by function. It does not define any structural features commonly possessed by members of the genus that distinguish them from the others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

The court also addressed the manner by which genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Applicant does not adequately describe the composition of the genes required for the claimed invention.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-27, 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of production of a polyhydroxyalkanoate, polyhydroxybutyrate-polyhydroxyvalerate containing 3-hydroxyhexanoate, by growing a bacterium transformed with phaC, phbAB, phbC, or phaJ genes, does not reasonably provide enablement for a method of production of a polyhydroxyalkanoate, polyhydroxybutyrate-polyhydroxyvalerate containing 3-hydroxyhexanoate, by growing a bacterium transformed with at least one bacterial transgene encoding; a PHA polymerase, a D-specific enoyl-CoA hydratase, a broad range reductase, a thiolase accepting acetoacetyl CoA, a thiolase specific for 3-ketohexanoyl CoA, a reductase active on 3-ketohexanoyl CoA and 3-hydroxyhexanoyl CoA, one or more fatty acid biosynthetic enzymes, enzymes forming a fatty acid oxidation complex, enzymes epimerizing S-3 hydroxyhexanoyl CoA, or enzymes reducing 3-ketohexanoyl CoA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicant claims a method of production of a polyhydroxyalkanoate, polyhydroxybutyrate-polyhydroxyvalerate containing 3-hydroxyhexanoate, by growing transgenic bacteria or transgenic plants encoding at least one transgene that encodes; a PHA polymerase incorporating C6 substrates, a D-specific enoyl-CoA hydratase, the enzymes in a butyrate fermentation pathway, a broad range reductase, a polymerase that accepts 3-hydroxyhexanoyl CoA, a thiolase accepting acetoacetyl CoA, thiolases specific for 3-ketohexanoyl CoA, a reductase active on 3-ketohexanoyl CoA and 3-hydroxyhexanoyl CoA, one or more fatty biosynthethic enzymes, and enzymes that epimerize S-3 hydroxyhexanoyl CoA from the *Pseudomonas putida* FaoAB complex.

Applicant teaches; PHBH synthesis from butyrate in *E. coli* transformed with genes encoding PHB polymerase from *A. caviae* (*phaC*), and β-ketoacyl-CoA reductase (*phbB*) and β-ketothiolase (*phbA*) from *R. Eutropha* (example 2), PHBH synthesis using a Fatty Acid Oxidation pathway in *E. coli* transformed with genes encoding D-specific enoyl-CoA hydratase from *A. caviae* (*phaJ*), and 3-ketohexanoyl-CoA reductase (*phbC*) from *R. Eutropha* (example 4), production of PHBH copolymers from butanol in *E. coli* expressing genes encoding PHB polymerase from *A. caviae* (*phaC*), and β-ketothiolase (*phbA*) and β-ketoacyl-CoA reductase (*phbB*) from *R. Eutropha* (the *A. caviae* PHB polymerase (*phaC*) and the *R. eutroph* Thiolase (*phbA*) and Reductase Genes (*phbB*)) (example 5).

Applicant does not teach a method of biological production of a polyhydroxyalkanoate, polyhydroxybutyrate-polyhydroxyvalerate containing 3-hydroxyhexanoate by growing a transgenic organism that uses all of the genes that comprise the generic categories set forth in the claims; a PHA polymerase incorporating C6 substrates, a D-specific enoyl-CoA hydratase, the enzymes in a butyrate fermentation pathway, a broad range reductase, a polymerase that accepts 3-hydroxyhexanoyl CoA, a thiolase accepting acetoacetyl CoA, thiolases specific for 3-ketohexanoyl CoA, a reductase active on 3-ketohexanoyl CoA and 3-hydroxyhexanoyl CoA, one or more fatty acid biosynthethic enzymes, and enzymes that epimerize S-3 hydroxyhexanoyl CoA from the *Pseudomonas putida* FaoAB complex. Furthermore, the applicant does not teach a method of production of a polyhydroxyalkanoate, polyhydroxybutyrate-polyhydroxyvalerate containing 3-hydroxyhexanoate, by growing transgenic plants.

Isolation of gene homologues from different bacterial organisms is highly unpredictable and requires significant guidance with respect to the probes, primers, hybridization and wash conditions and/or PCR reaction conditions. For example, in Boynton *et al.* (J. of Bacteriol. Vol. 178: 3015-3024, 1996), page 3021 column 1 lines 31-40, and column 2 lines 1-4, the authors show the degree of amino acid identity between crotonase, from *C. acetobutylicum*, compared to *C. difficile,* and *E. coli* to be 41% and 34% respectively. Furthermore, an analogous comparison of *eftA* and *eftB* genes from *C. acetobutylicum* and *P. denitrificans*, two of the microorganisms chosen as inventions in the specification, shows 30% and 36% amino acid sequence identity. The difference in nucleotide sequence identity, based upon the differences in amino acid identity, would introduce unpredictability in isolating the genes of the invention, other than those described in the examples. Based on the unpredictability in the art, the limited guidance set forth in the specification, and the breadth of the claims, one of average skill would have to resort to undue experimentation to work out the PCR conditions and primers to enable the invention.

Metabolic engineering of microorganisms or plants with non-native bacterial enzymes is highly unpredictable. The unpredictability arises from a lack of understanding of both the complex interactions of non-native protein assembly and the perturbation of regulation within the transgenic that may arise when engineered changes to metabolic pathways introduce novel interactions (De Luca, V., Ag Biotech News and Information. 1993 Vol. 5, No. 6, pp. 225N-229N) (page 225N, column 2, lines 6-8). Boynton *et al.* (J. of Bacteriol. Vol. 178: 3015-3024, 1996) show, (page 3021, Discussion, lines 17-22) that *C. acetobutylicum* butyryl Co-A dehydrogenase (BCD) activity was not detected in transformed *E. coli* extracts when grown under aerobic or anaerobic conditions. Since the gene is present, the authors suggest that the

enzyme is not functional in *E. coli* due to improper folding or is down regulated due to an unexpected autoregulatory control.

Considering the limited guidance in the specification showing bacterial production of PHA in *E. coli*, when compared to the broad palette of genes to be taken from the many different bacterial organisms and to be expressed in several different species of bacteria as well as the many different species from the plant kingdom as set forth in the claims, undue trial and error experimentation would be required to screen through cDNA and genomic clones, bacteria and plants transformed with different genes and gene combinations to identify those genes that could be successfully used in the claimed method of producing PHA containing 3-hydroxyhexanoate in bacteria and plants.

Given the lack of guidance, the limited working examples in the specification that reflect the breadth of the claims, and the unpredictability in the art, undue trail and error would be needed to practice the invention throughout the full scope of the claims. Therefore, the invention is not enabled.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 6, 8, 9, 15, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fukui *et al.* (J. of Bacteriol. Vol. 179: 4821-4830, 1997), in view of any of Sanders *et al.* (U.S. Pat. 5,238,833), Mascarenhas *et al.* (U.S. Pat. 5,470,727), or Huisman *et al.* (U.S. Pat. 6,316,262).

Applicant claims a method for the production of polyhydroxyalkanoates containing 3-hydroxhexanoate by growing a transgenic bacteria or transgenic plant encoding at least one transgene that encodes; a PHA polymerase incorporating C6 substrates, a D-specific enoyl-CoA hydratase, the enzymes in a butyrate fermentation pathway, a broad range reductase, a polymerase that accepts 3-hydroxyhexanoyl CoA, a thiolase accepting acetoacetyl CoA, thiolases specific for 3-ketohexanoyl CoA, a reductase active on 3-ketohexanoyl CoA and 3-hydroxyhexanoyl CoA, one or more fatty biosynthethic enzymes, and enzymes that epimerize S-3 hydroxyhexanoyl CoA from the *Pseudomonas putida* FaoAB complex.

Fukui discloses a method for producing polyhydroxyalkanoates containing 3-hydroxhexanoate by transformation of *Alacaligenes eutropus* and *Pseudomonas putida* with genes from *Aeromonas caviae* encoding PHA synthase (polymerase) and/or enoyl-CoA hydratase, as well as transgenic bacteria thereby obtained (Abstract; p. 4822, Tables 2-4).

Fukui does not disclose that the bacterial transgene is integrated into the chromosome.

Sanders discloses stable chromosomal expression of endogenous and exogenous polypeptides in *Bacilius* species (Abstract).

Mascarenhas discloses the chromosomal expression of heterologous genes in bacterial cells (Abstract, lines 1-6).

Huisman (U.S. Pat. 6,316,262) discloses stable integration of tDNA into the chromosome(s) of bacteria and plants for the production of stable yields of PHA (Abstract; column 2, lines 1-12)

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the invention of PHA production of Fukui to provide for stable chromosomal integration according to the techniques of Sanders, Mascarenhas, or Huisman in order to achieve stable and higher yields. One having ordinary skill in the art would have been motivated to integrate a transgene into the bacterial genome to stabilize the expression of bacterial or non-bacterial genes in bacterial cells for stable and effective expression, (Sanders *et al.*, column 14, lines 38-54) and (Mascarenhas *et al.*, column 1, lines 27-31); and thereby improve the yield of the PHAs in order to provide a more cost effective way of producing PHAs in transgenic biological systems (Huisman *et al.*, U.S. Pat. 6,316,262, column 3, lines 25-34 and column 11, lines 46-53).

7. Claims 11, 12, 13, and 14 rejected under 35 U.S.C. 103(a) as being unpatentable over Boynton *et al.* (J. of Bacteriol. Vol. 178: 3015-3024, 1996) in view of any of Sanders *et al.* (U.S. Pat. 5,238,833), Mascarenhas *et al.* (U.S. Pat. 5,470,727), or Huisman *et al.* (U.S. Pat. 6,316,262).

Boynton discloses a method for producing butyryl-CoA by transformation of *E. coli* with crotonase, butyryl-CoA dehydrogenase, and 3-hydroxybutyryl-CoA dehydrogenase from *C. acetobutylicum,* (p. 3016; lines 15-35).

Boynton does not disclose a bacterial transgene integrated into the chromosome.

Sanders discloses the stable chromosomal expression of endogenous and exogenous polypeptides in *Bacilius* species (Abstract).

Mascarenhas discloses the chromosomal expression of heterologous genes in bacterial cells (Abstract, lines 1-6).

Huisman (U.S. Pat. 6,316,262) discloses stable integration of tDNA into the chromosome(s) of bacteria and plants for the production of stable yields of PHA (Abstract; column 2, lines 1-12).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the invention of PHA production of Boynton to provide for stable chromosome integration according to the teachings of Sanders, Mascarenhas, or Huisman in order to achieve stable and higher yields. One having ordinary skill in the art would have been motivated to integrate a transgene into the bacterial genome to stabilize the expression of bacterial or non-bacterial genes in bacterial cells for stable and effective expression, (Sanders *et al.*, column 14, lines 38-54) (Mascarenhas *et al.*, column 1, lines 27-31); and thereby improve the yield of the PHAs in order to provide a more cost effective way of producing PHAs in transgenic biological systems (Huisman *et al.*, U.S. Pat. 6,316,262, column 3, lines 25-34 and column 11, lines 46-53).

8. All claims are rejected.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (703) 305-5417. The examiner can normally be reached on Monday-Friday 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (703) 306-3218. The fax phone numbers for the Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding, or if the examiner cannot be reached as indicated above, should be directed to the legal analyst, Kim Davis, whose telephone number is (703) 308-0009.

Russell Kallis Ph.D.
March 25, 2002

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